REMARKS

Status of Claims

New claim 26 is added. Basis for this claim is found throughout the specification as originally filed, including for example page 26, line 8. No new matter is added. Following entry of the new claim, claims 1-7, 18, 19, and 23-26 will be pending.

The rejection under 35 U.S.C. §103 should be withdrawn

In the Office Action, the Office has maintained the rejection of claims 1-7 and 18-25 under 35 U.S.C. §103(a) as being allegedly unpatentable over Muller et al., U.S. Patent No. 6,020,358 ("Muller") in view of Tobinick, U.S. Patent No. 6,425,787 ("Tobinick") and D'Amato U.S. Patent No. 6,235,756 ("D'Amato"). The Office refers to the Office Action of November 13, 2008, which alleges that: (1) Muller allegedly teaches the use of the claimed compounds as TNF alpha reducing compounds; (2) Tobinick allegedly teaches the use of TNF alpha blockers or antagonists for the treatment of macular degeneration; and (3) D'Amato teaches the use of the claimed secondary components. Office Action page 2. The Office has also required that Applicant "compare the claimed compound with the closest structurally similar TNF alpha inhibitor disclosed by the prior art and to show advantage in terms of treating macular degeneration." Office Action, page 2.

I. The rejection is improper

At the outset, Applicant reiterates that the instant claims are not *prima facie* obvious over Muller in view of Tobinick and D'Amato for the reasons set forth in all of Applicant's Responses of record.[1] Applicant also reiterates that the previously presented unexpected results, which shows that the instant compound performed as well as or even better than Lucentis® (a current standard of care in connection with the treatment of wet age-related macular degeneration), are more than sufficient to rebut any alleged *prima facie* case of obviousness. "When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence."

[1] Including Applicant's Response filed March 5, 2009.

In re Sullivan, 498 F.3d 1345, 1351 (Fed. Cir. 2007). Such rebuttal evidence includes "evidence of unexpected results." *Id.*, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007).

Applicant also respectfully submits that the requirement to compare the instant compound to the "closest structurally similar TNF alpha inhibitor" is improper. First, the phrase "closest structurally similar" is vague and ambiguous. Depending on the context or how one defines "structurally similar," two compounds can be deemed structurally similar in one scenario yet structurally dissimilar in another. Therefore, it is impossible for Applicant to determine what compound is "structurally similar," much less what compound is the "closest" structurally similar compound to comply with the Examiner's requirement. Second, the Examiner seems to be seeking the inventor's view of what, in hindsight, is the closest structurally similar compound. Even assuming it was clear as to what is meant by that term, such is an improper rejection. The Examiner has the burden of stating what is the closest structurally similar compound. For this reason alone, the rejection should be withdrawn.

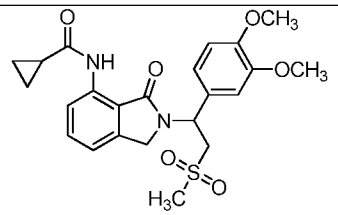
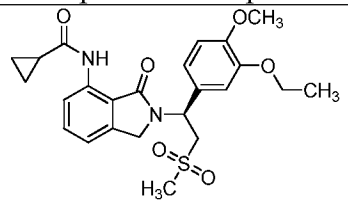
II. The recited compound exhibits unexpected properties that rebuts any alleged *prima facie* case of obviousness

In any event, since the evidence of record has not been found persuasive by the Examiner, Applicant submits herewith a Declaration by Peter H Schaffer, Ph.D. under 37 C.F.R. §1.132 ("Declaration A")[2] that *further* demonstrates the instant compound's uniqueness in the treatment of macular degeneration. First, as presented in Declaration A and shown below, the instant compound was surprisingly found to be approximately 50 times more potent in inhibiting vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) proliferation and approximately 170 times more potent in inhibiting TNF-alpha than N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisoindolin-4-yl)cyclopropanecarboxamide[3],("comparative compound"). Anti-VEGF and angiogenesis therapy

[2] Attached hereto as Exhibit A.

[3]As discussed above, the term "closest structurally similar" is vague and ambiguous, and it is unclear to Applicant what is being requested by the Office. Nevertheless, data for the comparative compound are being submitted since the Examiner's position appears to be that Muller is the closest prior art reference. To elaborate, the Examiner has taken the position that Muller discloses the instant compound because one can choose CH_2 for Y, NR^8R^9 for R^1, H for R^2, R^3, R^4, and R^8, methoxy for R^5, ethoxy for R^6, methyl for R^7, COR^{10} for R^9, cyclopropyl for R^{10}, and the (S)

is accepted by those skilled in the art to be an effective form of macular degeneration treatment, as evidenced by Pieramici *et al*, *Eye*, 22, 1330-1336 (2008).[4]

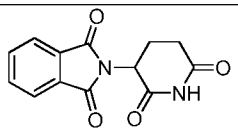
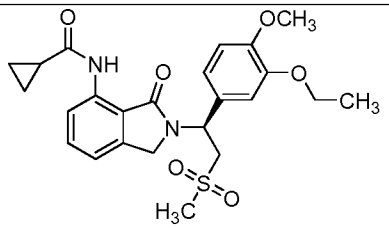
Compound	TNF-alpha inhibition IC_{50} (nM)	VEGF induced HUVEC inhibition IC_{50} (nM)
 comparative compound	8600	2600
 instant compound	**50.6**	**50**

Second, it was surprisingly found that while oral administration at 100 mg/kg of thalidomide[5] does *not* significantly inhibit angiogenesis in a VEGF induced mouse corneal micropocket model, oral administration of the instant compound at 25 mg/day significantly inhibits angiogenesis.

isomer. If one follows the Examiner's rationale, the comparative compound is also disclosed by Muller, except that methoxy is chosen for R^6 and no stereochemistry is defined. Applicant does not take the position that the comparative compound is the "closest structurally similar" compound. Again, it is impossible for Applicant's to make that determination. Further, Applicant's position is that neither the instant compound nor the comparative compound is disclosed by Muller.

[4] Attached hereto as Exhibit B.

[5] Applicants do not take the position that thalidomide is structurally similar to the instant compound. However, as thalidomide is reported to be a TNF alpha inhibitor in Sampaio *et al.*, *J. Exp. Med.*, 173, 699-703 (1991), Applicant submits these data in view of the Examiner's requirement to submit data comparing the instant compound to "the closest structurally similar TNF alpha inhibitor disclosed by the prior art."

Compound	Effect on Angiogenesis
 thalidomide	No significant effect
 instant compound	Significant inhibition

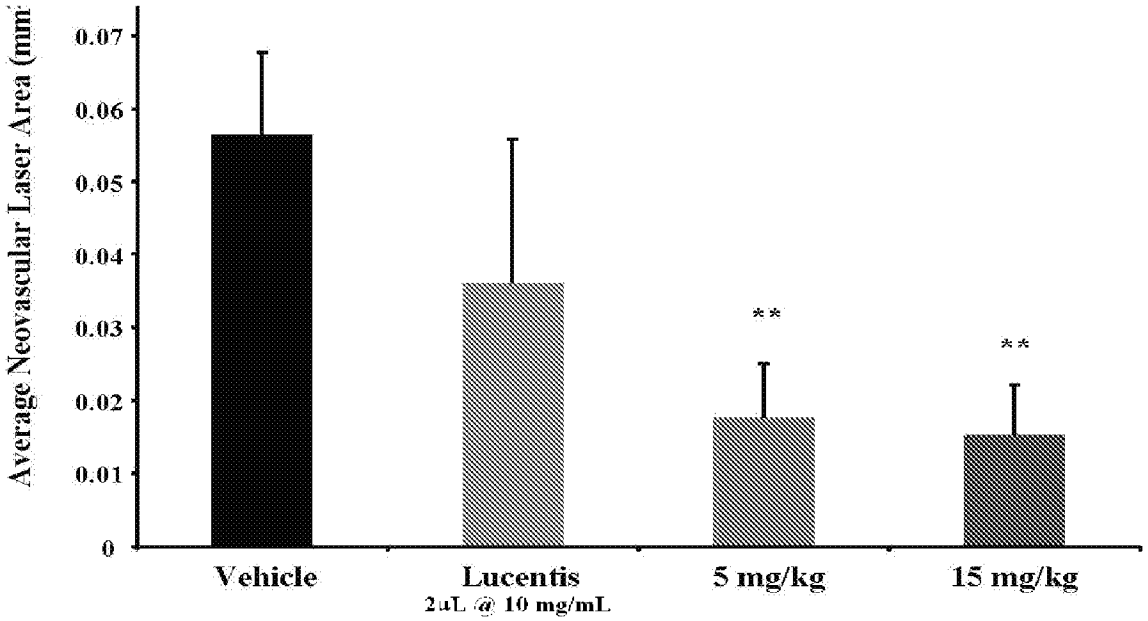
Applicants respectfully submit that the results presented above could not have been predicted by those skilled in the art at the time of the invention and are significant and surprising. The presented evidence constitute unexpected results that are sufficient to overcome any *prima facie* case of obviousness.

III. Summary of Applicant's Evidence of Unexpected Results Presented to Date

Applicant has provided more than enough evidence of unexpected results to overcome the Examiner's alleged case of *prima facie* obviousness, which itself is legally improper. Indeed, in Applicant's Response filed October 15, 2008, Applicant submitted a declaration from Peter H. Schafer, Ph.D. under 37 C.F.R. §1.132 ("Declaration B")[6], which describes experiments that were performed to evaluate the *in vivo* activity of the instant compound in the treatment of macular degeneration. As explained in Declaration B, the oral administration of the instant compound to mice unexpectedly resulted in remarkably higher inhibition of laser-induced choroidal neovascularization compared to the intravitreal injection of Lucentis®, which is a FDA-approved drug for the treatment of wet age-related macular degeneration. Further, the oral administration of the instant compound to rats resulted in similar inhibition of laser-induced choroidal neovascularization compared to intravitreal injection of Lucentis®. The results are summarized in the figures below.

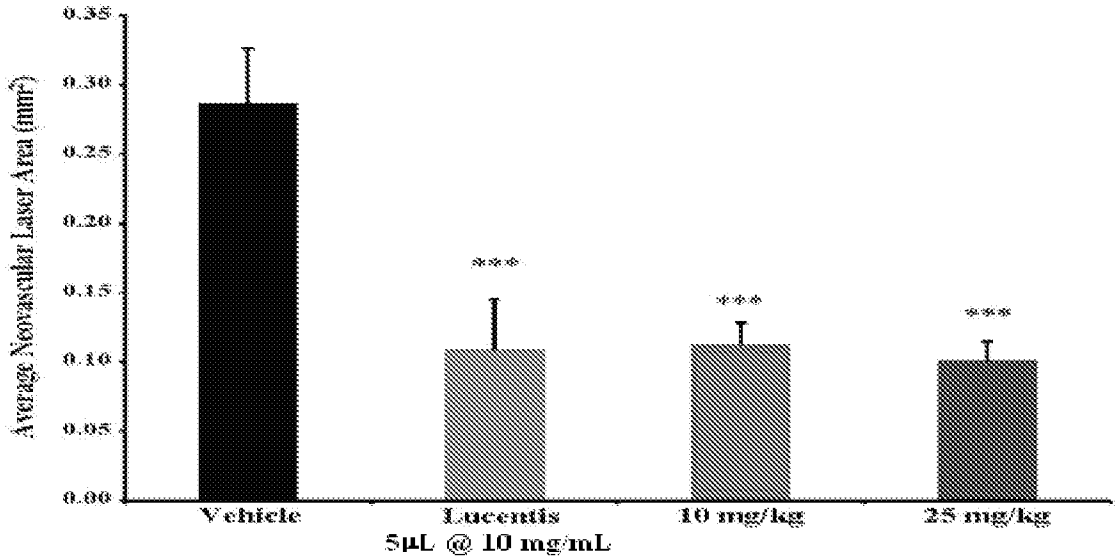
[6] Attached hereto as Exhibit C.

Histogram of Instant Compound on Laser-Induced Choroidal Neovascularization Areas in Mice



Asterisks (**) represent significance levels of P<0.002 vs. vehicle control.

Histogram o Instant Compound on Laser-Induced Choroidal Neovascularization Areas in Rats



Asterisks (**) represent significance levels of P<0.0001 vs. vehicle control.

Thus, in sum, the following unexpected results have been provided:

(1) the instant compound is surprisingly ~50 times more potent in inhibiting vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) proliferation than N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisoindolin-4-yl)cyclopropanecarboxamide;

(2) the instant compound is surprisingly ~170 times more potent in inhibiting TNF-alpha than N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisoindolin-4-yl)cyclopropanecarboxamide;

(3) the oral administration at 100 mg/kg of thalidomide does *not* result in significant inhibition of angiogenesis in a VEGF induced mouse corneal micropocket model, while the oral administration of the instant compound at 25 mg/day surprisingly results in significant inhibition angiogenesis;

(4) the oral administration of the instant compound to mice unexpectedly resulted in remarkably higher inhibition of laser-induced choroidal neovascularization compared to the intravitreal injection of Lucentis®, which is a FDA-approved drug for the treatment of wet age-related macular degeneration; and

(5) the oral administration of the instant compound to rats resulted in similar inhibition of laser-induced choroidal neovascularization compared to intravitreal injection of Lucentis®.

The unexpected results above are more than sufficient to rebut any alleged *prima facie* case of obviousness. Applicant, therefore, respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

Fees

A fee of $130.00 is believed due for the one-month extension of time. Further, a fee of $810.00 is believed due for the Request for Continued Examination. These fees are submitted concurrently herewith via EFS. If any additional fees are due for the submission of this paper or to avoid abandonment of this application, please charge them to Deposit Account No. 50-3013.

Respectfully submitted,

Date: **February 1, 2010**

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